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SEASONAL VARIATIONS OF NASAL RESISTANCE IN ALLERGIC RHINITIS AND ENVIRONMENTAL POLLEN COUNTS II: EFFICACY OF PRESEASONAL THERAPY

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We gave Mao-bushi-saishin-to, a Chinese blended medicine, and azelastine to an adult patient with hay fever due to Japanese cedar pollen and measured nasal resistance and ambient floating pollen counts throughout the time of Japanese cedar pollination in separated years. In the patient Mao-bushi-saishin-to was effective against preseasonal increases in nasal airway resistance but could not control severe episodes of allergic rhinitis caused by high dose exposure to Japanese cedar pollen and also perhaps caused by a priming effect. Azelastine inhibited both pre- and post-seasonal increases in nasal airway resistance but not only on high pollen counts days.

We previously found that in a subject with Japanese cedar pollinosis not only amounts of floating pollens and priming effect (nonspecific hypersensitivity of the nasal mucosa following environmental pollen exposure),[1,2] but also the circannual rhythm might relate to variability of nasal patency.[3]

Nasal airway resistance of the previously reported patient with seasonal allergic rhinitis due to Japanese cedar pollen begins increasing 1 or 2 weeks prior to the beginning of Japanese cedar pollination. The phenomenon might relate to a circannual rhythm of the immune, autonomic, and/or endocrine system. Preseasonal management of the phenomenon may contribute to effective therapy for hay fever due to Japanese cedar pollen.

Mao-bushi-saishin-to (Ma-Huang-Fu-Zi-Xi-Xin-Tang), a Chinese blended medicine, so-called kampo preparation, has been employed for the treatment of allergic rhinitis.[4,5] In fundamental pharmacological studies, Mao-bushi-saishin-to has both anti-allergic activities and β_2-adrenergic stimulant effect.[6-8]

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Azelastine is an anti-allergic drug with potent histamine H_1-receptor blocking properties[9] and also inhibits mediator (including LTC_4/D_4 and histamine) release from mast cells.[10-12] Clinically, azelastine is more effective in Japanese cedar pollinosis patients if employed preseasonally.[13] Azelastine, furthermore, may prevent down regulation observed during β-agonist administration by increasing the number of β-adrenoceptors.[14]

In this communication, we gave Mao-bushi-saishin-to in 1990 and azelastine in 1991 preseasonally to an adult patient with allergic rhinitis due to Japanese cedar pollen, and measured his nasal airway resistance and environmental pollen counts during the period between January and July in the both years.

MATERIALS AND METHODS

Subject. A voluntary adult male subject who has suffered from allergic rhinitis to Japanese cedar pollen since 1978 was studied. Physical examination revealed a deviated nasal septum to the right side but he had no apparent symptoms from this. His prick skin test responses to ash, birch, hazel, elm, poplar, oak, willow, maple, beech, sycamore, Canadian cedar, Canadian pine (Bencard, Ontario), and mite (Torii Co., Ltd., Japan), and intradermal skin tests to Japanese pine, gramina (a type of Japanese grass), alternaria, candida, and house dusts (Torii, Co., Ltd.) were negative but his intradermal injection skin reaction to Japanese cedar (Torii Co., Ltd.) was strongly positive (wheal diameter more than 20×20 mm). His concurrent RAST score of Japanese cedar was 5.90 PRU/ml (+++) and serum total IgE level was 45 IU/ml.

Nasal airway resistance measurement. Unilateral nasal airway resistance (cmH_2O/liter/sec at peak flow point) on expiration was measured by active anterior rhinomanometry with a nasal nozzle using Rhinorheograph MPR-2100 (manufactured by Nihon-Kohden Co., Ltd., Japan). Total nasal airway resistance is calculated from each measured unilateral nasal airway resistance according to modified Ohm's law for parallel resistors.[15]

Assessment course. Assessments were carried out every hour in a day from 9:00 a.m. to 5:00 p.m. once a week, throughout the Japanese cedar pollinating season. Mean total nasal airway resistance of the assessing day was employed as a representative of the resistance of each assessing day.

The subject always spent each assessing day with light desk work under constant environmental temperature with air-conditioning in his office throughout the testing season.

The patient was given Mao-bushi-saishin-to extract capsules orally three times a day (six capsules/day) during the period from January 19th 1990 to March 8th 1990, and was given azelastine tablet (1 mg) orally twice daily during the period from January 10th 1991 to April 30th 1991.

Sampling and counts of pollens. Environmental floating pollens around the

subject's residence were sampled and counted with Durham's pollen sampler on the roof of his office building (grains/cm^2).

We compared the mean total nasal airway resistance on expiration of each assessing day with environmental pollen counts.

RESULTS

Total pollen counts of Japanese cedar including Japanese cypress in 1990 was 3,392/cm^2 which was a high pollen season. The mean total nasal airway resistances of the patient in 1990 and daily Japanese cedar pollen counts as shown in Fig. 1, and daily total pollen counts in Fig. 2, respectively. Also the variability of mean total airway resistance with no medication for allergic rhinitis in 1986 was overlapped on each figure as a contrast. Preseasonal high values of mean total nasal airway resistance for 1 or 2 weeks possibly caused by circannual endogenous rhythm might be suppressed by the preseasonal administration of Mao-bushi-saishin-to. But after the first day of high Japanese cedar pollen counts the mean total nasal airway resistance increased with severe symptoms of allergic rhinitis and increased resistance was maintained until 2 months after the end of Japanese cedar pollination.

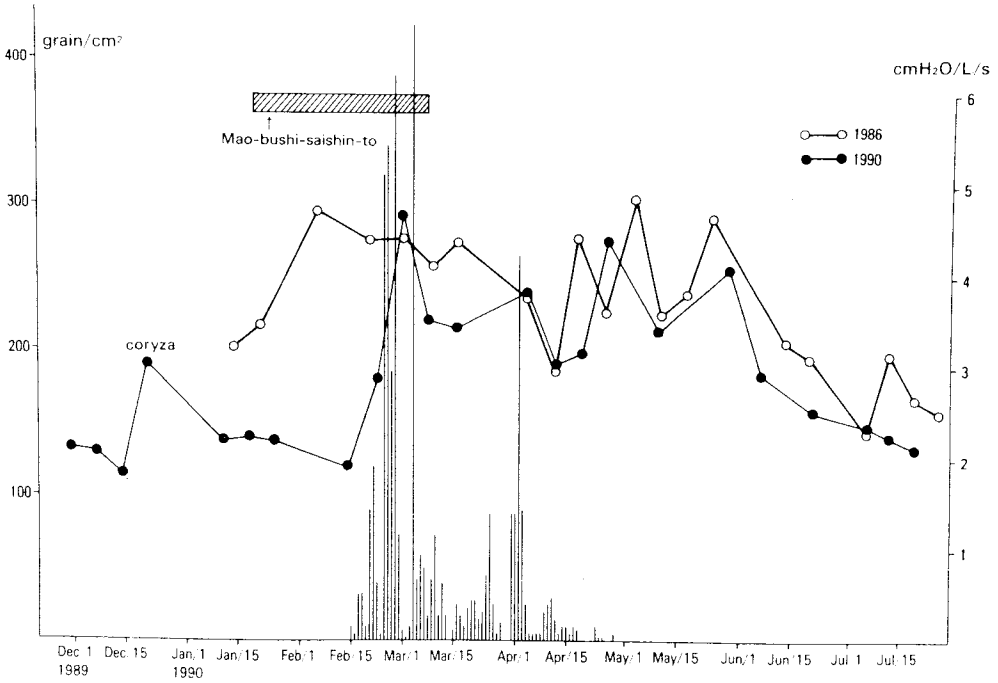

Fig. 1. Alteration of mean bilateral nasal airway resistance at peak flow on expiration at peak flow and daily Japanese pollen counts in Nagoya, Japan, during the period between November 30th 1989 and July 19th 1990. Alteration of mean bilateral nasal airway resistance in 1986 was overlapped on the figure as a contrast.

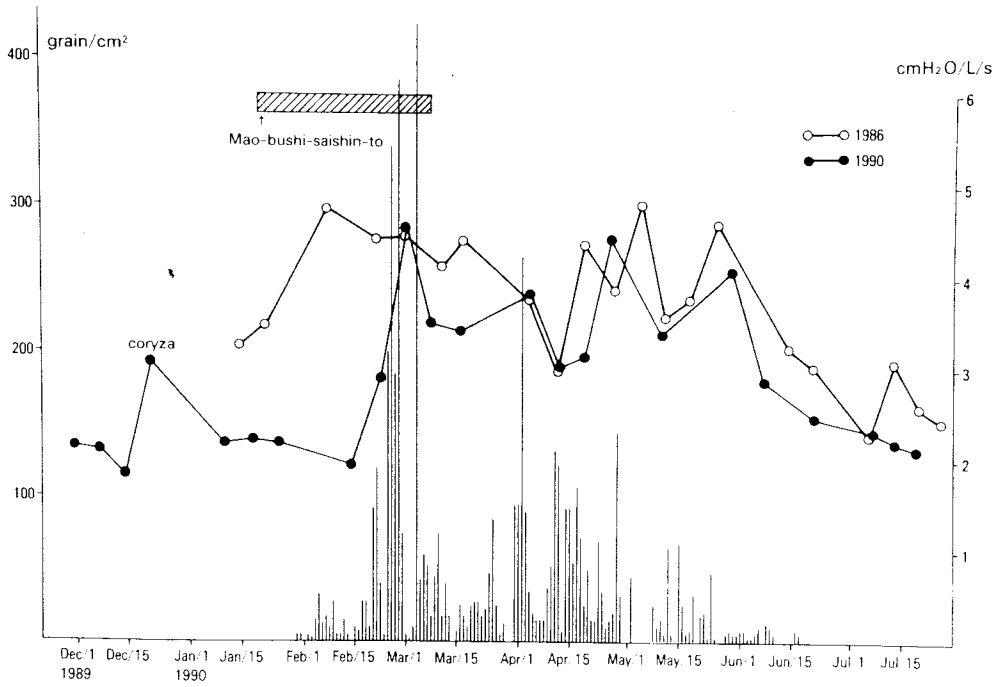

Fig. 2. Alteration of mean bilateral nasal airway resistance at peak flow on expiration and daily total floating pollen counts in Nagoya, Japan, during the period between November 30th 1989 and July 19th 1990. The alteration of mean bilateral nasal airway resistance in 1986 was overlapped on the figure as a contrast.

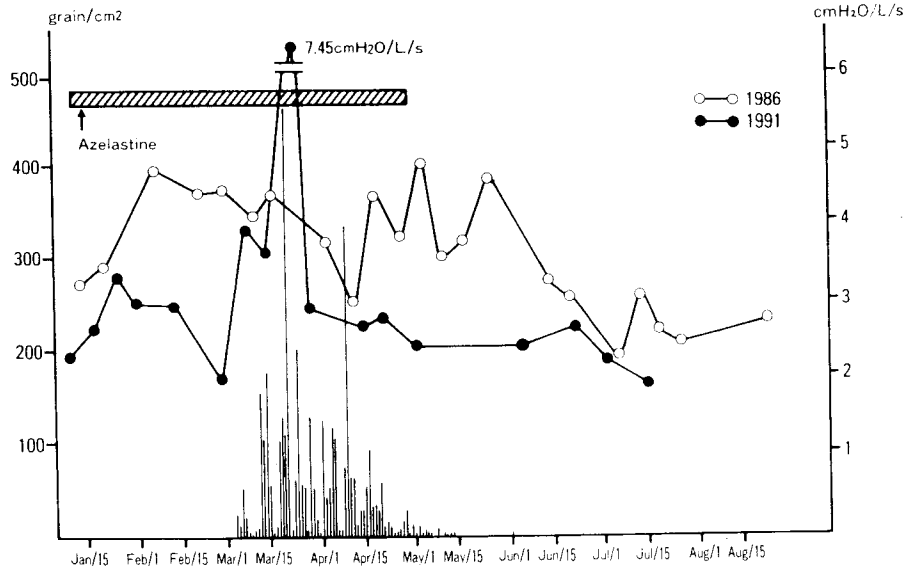

Fig. 3. Alteration on mean bilateral nasal airway resistance at peak flow on expiration and daily Japanese pollen counts in Nagoya, Japan, during the period between January 10th 1991 and July 5th 1991. Alteration of mean bilateral nasal airway resistance in 1986 was overlapped on the figure as a contrast.

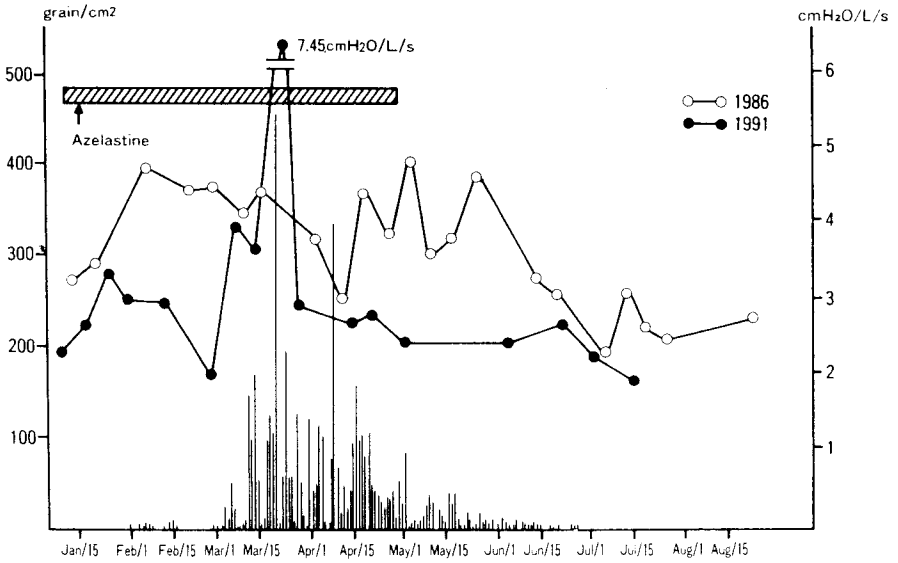

Fig. 4. Alteration on mean bilateral nasal airway resistance at peak flow on expiration and daily total floating pollen counts in Nagoya, Japan, during the period between January 10th 1991 and July 5th 1991. Alteration of mean bilateral nasal airway resistance in 1986 was overlapped on the figure as a contrast.

After the first day of high Japanese cedar pollen counts, peroral antihistamine and topical steroid were required for control of the severe symptoms. Use of only Mao-bushi-saishin-to was not able to manage the severe symptoms due to high dose exposure to Japanese cedar pollens and likely also the priming effect in the patient.

In 1991, also it was a high Japanese cedar pollen season including Japanese cypress (3,436/cm^2). The relationship between alteration of mean nasal airway resistances and Japanese cedar pollen counts, and total pollen counts were shown in Fig. 3 and Fig. 4, respectively. The alteration of mean nasal airway resistance with no medication for the allergic rhinitis in 1986 was overlapped again on each figure as a contrast. Pre- and seasonal increases on mean total nasal airway resistances were clearly inhibited by use of azelastine even with large exposures to aeroallergen as shown in Fig. 3. Only on extremely high Japanese cedar pollen counts days increased nasal airway resistances occurred in the patient. The patient needed no other anti-histamine nor topical steroid during the assessing period.

DISCUSSION

We previously demonstrated the relationship between spontaneous variability of nasal patency in a patient with seasonal allergic rhinitis due to Japanese cedar and the floating pollen counts throughout the pollinating season.[3] In the season of high Japanese cedar pollen counts (1986) mean nasal airway resistance started to

increase approximately 2 weeks prior to pollination of Japanese cedar, and maintained a high mean resistance until approximate 2 months after the end of Japanese cedar pollination. In the season of a low pollen count (1989), the mean nasal airway resistance was increased during the season but decreased in a short period after the Japanese cedar pollination season. In the season of no exposure to the environmental antigen because the subject lived out of Japan, the mean nasal airway resistance was relatively increased closely in phase with the Japanese cedar pollinating season in Japan of the year (1988).

In each year, mean nasal airway resistances started to increase 2 weeks prior to Japanese cedar pollinating season in any aeroantigen conditions. The preseasonal increase of nasal airway resistance is not considered a priming effect because the phenomenon can take place without environmental antigen exposure. The phenomenon may be due to a circannual rhythm of the immune, endocrine, or autonomic systems. Thus preseasonal management of the phenomenon may contribute to effective therapy for seasonal allergic rhinitis.

Effect of preseasonal treatment in pollinosis has been reported.[13,14] In this study we employed Mao-bushi-saishin-to, a Chinese blended medicine, and azelastine for preseasonal therapy in the patient with allergic rhinitis due to Japanese cedar studied previously without therapy by us because these medicines have both anti-allergic effect and β_2-adrenergic stimulant effect.[6,16] Takayasu et al suspected that autonomic imbalance took place following blockade of β-adrenergic receptor by self-antibody to β-adrenergic receptor.[17] Autonomic imbalance might lead to reduction of the threshold of clinical response to antigen–antibody reaction and inflammation in the nasal mucosal tissue in nasal allergy.

Mao (crude Ephedra extract) of Mao-bushi-saishin-to can increase adrenergic activity (β_2-adrenergic receptor stimulation) represented by alkaloid fraction.[6] D-Pseudoephedrine of Mao exhibits the relaxing effect on bronchial smooth muscle as similar to *l*-ephedrine. Respiratory airway resistance increased by histamine can be inhibited by *d*-pseudoephedrine without influence on blood vascular system.[18] Mao and saishin of Mao-bushi-saishin-to inhibit allergen induced mast cell-mediator release.[7] Clinically, Ukai et al[4] and Nakajima et al[5] reported that Mao-bushi-saishin-to was useful for treatment of allergic rhinitis.

In this study, Mao-bushi-saishin-to appeared to be effective against preseasonal increases in nasal airway resistance but not against severe episodes of allergic rhinitis. Preseasonal increases in nasal airway resistance might be suppressed likely by the adrenergic receptor stimulation of Mao. However, Mao-bushi-saishin-to was not able to control severe symptoms and oral anti-histamines and topical steroids were required for treatment of the severe symptoms in the subject. Takayasu et al have recommended combination therapy of oral steroid and azelastine for control of symptoms due to high dose exposure to Japanese cedar.[17] Furuya et al also reported preseasonal administration of azelastine was more effective than when given to relieve symptoms which were already severe.[13] Thus we employed

azelastine against Japanese cedar pollinosis the next year in the same subject.

Azelastine is a histamine H_1-receptor blocker and also has been shown to inhibit histamine release from mast cells and leukocytes.[11] In addition Katayama et al have demonstrated with a radioimmunoassay, that azelastine inhibits the release of leukotriene C_4/D_4 from leukocytes.[12] Other inhibitory effects of azelastine include those on O^{2-} production in polymorphonuclear leukocytes and PAF (platelet-activating factor)-acether–induced PGE_2 (prostaglandin E_2) release from macrophage.[19] Azelastine also may prevent down regulation observed during β-agonist administration by increasing the number of β-adrenoceptors.[14]

In the patient, pre- and postseasonal increases of mean nasal airway resistances were clearly inhibited while taking azelastine. High values of nasal airway resistance due to high dose exposure to aeroallergen were not able to be prevented by anti-allergy effects of azelastine but the patient never needed any other medicines for relief from symptoms throughout the testing season. The preseasonal increase of nasal airway resistance might be prevented by the effect of azelastine increasing the number of β-adrenoceptors. Anti-leukotriene C_4/D_4, anti-PAF, and anti-O^{2-} activities of azelastine may prevent accumulation of eosinophils in the nasal mucosa or damage to the nasal mucosal epithelium, and consequently, might suppress nonspecific hypersensitivity of the nasal mucosa. Those effects of azelastine may be causes of prevention of pre- and postseasonal increase of nasal airway resistance in the patient with Japanese cedar pollinosis.

It is difficult to mention an entire conclusion as a result of a single case investigation, but we consider that the result of the study may be an interesting for presentaion.

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